Eksakta : Berkala Ilmiah Bidang MIPA
VOLUME 26 NO 03 2025, pp 384-395
ISSN : Print 1411-3724 — Online 2549-7464
DOI : https://doi.org/10.24036/eksakta/vol26-iss03/621

Eksakta
Berkala Ilmiah Bidang MIPA
http://www.eksakta.ppj.unp.ac.id/index.php/eksakta

Review

Molecular Pathway of Phytochemicals in Preventing Sarcopenia

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Article Info

Article history :
Received August 25, 2025
Revised September 08, 2025
Accepted September 15, 2025
Published September 30, 2025

Keywords :
Sarcopenia, phytochemicals, molecular pathways, muscle ageing

Abstract. Sarcopenia, the age-related decline in muscle mass and function, poses a significant global health challenge. This systematic review synthesizes evidence from preclinical studies published between 2020 and 2025 to elucidate the molecular pathways through which phytochemicals prevent sarcopenia. Following PRISMA guidelines, a systematic search of databases identified 16 eligible studies. The analysis reveals that phytochemicals, including flavonoids, polyphenols, and botanical extracts, mitigate muscle atrophy by concurrently enhancing anabolic signaling via the IGF-1/PI3K/Akt/mTOR axis, suppressing proteolysis, improving mitochondrial biogenesis, and reducing oxidative stress and inflammation. Notably, combinatorial formulations and multi-target extracts demonstrate superior efficacy. The review concludes that phytochemicals represent a promising multi-targeted strategy against sarcopenia; however, this promising potential necessitates future validation through standardized clinical trials to establish efficacy and safety in human populations.

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1. Introduction

1.1. Sarcopenia

Sarcopenia, also known as a multifactorial geriatric syndrome, is characterized by a progressive decline in skeletal muscle quantity, strength, and functional capacity. This condition increases the likelihood of falls, frailty, disability, impaired quality of life, and mortality in older adults. Its prevalence continues to rise globally in parallel with population ageing [1].

In Indonesia, the older adult population already exceeds 28 million and is projected to increase sharply in the coming decades. This demographic trend underscores sarcopenia as an emerging national health challenge [2]. Epidemiological studies estimate its prevalence at approximately 19.6% (17.1% in women and 23.1% in men), with higher rates observed among individuals aged ≥65 years [3].

Sarcopenia frequently coexists with obesity, a condition termed sarcopenic obesity [1]. This combination exacerbates metabolic dysfunction, accelerates muscle degeneration, and places an additional burden on healthcare systems. At the molecular level, sarcopenia involves a disrupted balance between anabolic and catabolic processes, mitochondrial dysfunction, chronic low-grade inflammation, and redox imbalance [4],[5].

Impaired activation of the IGF-1/PI3K/Akt/mTOR pathway restricts protein synthesis, while upregulation of catabolic regulators such as myostatin, MuRF1, and MAFbx enhances proteolysis [6]. In parallel, mitochondrial abnormalities increase reactive oxygen species (ROS) accumulation, reduce respiratory capacity, and trigger apoptotic cascades. These processes collectively drive muscle fiber loss and functional decline, particularly under metabolic stress such as obesity [7],[8].

1.2. Molecular Pathways of Phytochemicals

Sarcopenia is driven by dysregulation of molecular networks governing muscle homeostasis, including protein turnover, energy metabolism, oxidative balance, and inflammatory signaling [9]. Anabolic resistance through impairment of the IGF-1/PI3K/Akt/mTOR pathway is a key factor in muscle loss. Conversely, hyperactivation of catabolic pathways such as the ubiquitin–proteasome system (UPS) and autophagy accelerates protein degradation [10],[11].

Chronic low-grade inflammation, or inflammaging, further worsens these mechanisms by activating NF-κB and promoting the secretion of cytokines such as TNF-α and IL-6. Mitochondrial dysfunction also aggravates oxidative stress and apoptotic signaling, resulting in the progressive loss of contractile fibers [12],[13]. Given these complex mechanisms, interventions targeting multiple pathways simultaneously are urgently needed.

Phytochemicals, bioactive compounds derived from plants, have emerged as promising candidates to modulate these pathways. Flavonoids such as quercetin and luteolin suppress NF-κB activation and reduce cytokine production, thereby attenuating inflammation-induced muscle catabolism [14],[15]. Epigallocatechin gallate (EGCG) activates the SIRT1–PGC-1α axis, enhancing mitochondrial biogenesis, energy balance, and resistance to oxidative damage [16].

Similarly, curcumin from Curcuma longa and sulforaphane from cruciferous vegetables strengthen the Nrf2–ARE antioxidant response, protecting myotubes from apoptosis and preserving muscle fiber integrity [17]. Clinical evidence further supports the potential of phytochemicals as nutritional strategies against sarcopenia. A recent meta-analysis reported that supplementation improved muscle mass and performance by regulating anabolic and catabolic pathways [18].

In Indonesia, Hibiscus sabdariffa Linn. (HSL), commonly consumed as roselle tea, is noteworthy. Rich in flavonoids and anthocyanins, it exhibits antioxidant, anti-inflammatory, and metabolic regulatory activities in both preclinical and clinical studies. However, its role in mitigating sarcopenia, especially in ageing populations and sarcopenic obesity, remains underexplored.

1.3. Literature Gap and Objective of the Review

Previous reviews on phytochemicals and sarcopenia remain fragmented, lacking a comprehensive synthesis that integrates how these compounds simultaneously regulate anabolic signaling, proteolysis, mitochondrial function, inflammation, and oxidative stress, which constitutes the current literature gap[2],[18–20].

The objective of this review is to synthesize recent evidence on molecular pathways targeted by phytochemicals in the prevention of sarcopenia and to highlight gaps that may guide future translational and clinical research.

2. Method

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21]. Literature searches were conducted in PubMed, Scopus, and Web of Science databases for studies published between January 2020 and July 2025. Search terms combined keywords related to sarcopenia (e.g., "sarcopenia," "muscle atrophy," "sarcopenic obesity") and phytochemicals (e.g., "polyphenols," "flavonoids," "curcumin," "resveratrol," "quercetin," "epigallocatechin gallate").

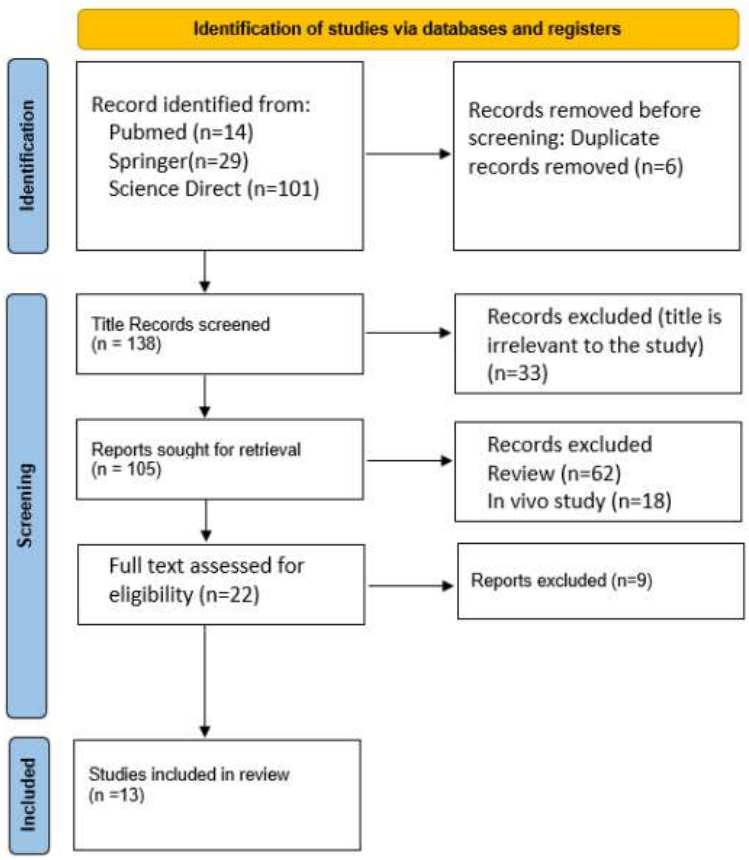

Figure 1 Article selection based on PRISMA flow

Inclusion criteria were: (i) experimental, preclinical, or clinical studies investigating phytochemicals in the context of sarcopenia or muscle ageing; (ii) studies reporting molecular or mechanistic outcomes (e.g., signaling pathways, mitochondrial function, oxidative stress, inflammatory response); (iii) publications in English. Exclusion criteria included reviews, conference abstracts, editorials, and studies unrelated to sarcopenia.

Study quality was assessed using SYRCLE's risk of bias tool for animal studies. Only studies judged as low or moderate risk of bias were included in the synthesis [22]. Data extraction included: study type, species or population, sample size, type and dose of phytochemical, duration of intervention, experimental model, and molecular outcomes. Findings were synthesized narratively, with emphasis on comparisons across phytochemicals and critical appraisal of methodological strengths and limitations.

3. Results and Discussion

In total, 144 articles were initially identified from PubMed (n = 14), Springer (n = 29), and ScienceDirect (n = 101). Following the removal of six duplicates, 138 articles remained for title screening. Of these, 33 articles were excluded due to irrelevance, leaving 105 articles for further evaluation. At this stage, 83 articles were excluded, comprising 62 review papers, 18 in vivo studies, and 3 classified under other categories. Consequently, 22 articles proceeded to full-text assessment, of which 9 were excluded because they did not meet the eligibility criteria. Ultimately, 13 articles were selected as eligible and included in the further thematic analysis.

The following table (Table 1) summarizes the key characteristics extracted from the included studies investigating the effects of various phytochemicals on muscle health and sarcopenia. It outlines essential details such as the type of study, species or population studied, sample sizes, types and dosages of phytochemicals used, duration of interventions, experimental models employed, and the main molecular outcomes assessed. This overview facilitates a clear comparison across different research designs and highlights the range of methodologies and endpoints utilized in this field.

Table 1. Characteristics of studies

Study Type	Species Population	Sample Size	Phytochemical Type	Dosage	Duration	Experimental Model	Ref
In vivo animal study	Male Wistar rats, 15 mo	47 total	Apigenin (flavonoid)	50 mg/kg/day, oral	88 days	Diet-induced obesity (high-calorie diet)	[23]
In vivo animal study	Rats with metabolic syndrome (MetS)	Not explicitly stated (MetS & control groups)	Resveratrol + Quercetin	N/A	N/A	Sarcopenic obesity induced by MetS	[24]
In vivo animal study	C57BL/6J mice, young (3–6 mo) & old	Not specified, multiple groups (Ctrl, HES 5, HES 10)	Hesperidin (flavanone)	5 or 10 mg/kg/day, oral.	8 weeks	Natural aging-induced sarcopenia	[25]
In vivo animal study	Middle-aged male C57BL/6J mice (40 wks)	n=8/group; 5 groups (total 40)	Agastache rugosa extract (AR) (tilianin, rosmarinic acid)	100 or 200 mg/kg/day, oral; ±voluntary wheel running	4 weeks	Aging-related anabolic resistance model	[26]
In vivo animal study	Male BALB/c mice (8 weeks old)	50 mice, 5 groups	Propolis alcohol extract (polyphenols, flavonoids, CAPE, etc.)	100 or 300 mg/kg/day, oral (with D-gal 125 mg/kg injections)	8 weeks	D-galactose–induced skeletal muscle senescence	[27]
In vivo animal study	Aged male Sprague–Dawley rats (15 mo)	23 rats, 5 groups	Shiikuwasha extract (nobiletin,	1% diet for 19 days; DEX injection 750 µg/kg/day.	5 days	Dexamethasone-induced muscle atrophy	[28]

Study Type	Species Population	Sample Size	Phytochemical Type	Dosage	Duration	Experimental Model	Ref
			tangeretin; polyphenols)				
In vivo animal study	C57BL/6 mice (3 mo & 22 mo, aged model)	Not clearly stated (young ctrl, aged ctrl, + LNX 10 & 100 mg/kg groups)	Lignan-enriched nutmeg extract (LNX)	10 or 100 mg/kg/day, oral.	3 weeks	Aging + exercise performance tests	[29]
In vivo animal study	Aged C57BL/6J mice (18 mo)	Not specified (3 groups: aged control, KPE 100 mg/kg, KPE 200 mg/kg)	Kaempferia parviflora extract (KPE) (std. 8.58% DMF)	100 or 200 mg/kg/day, oral.	8 weeks	Natural aging-induced sarcopenia	[30]
In vivo animal study	Male ICR mice (7 weeks)	n=33 (9 CON, 8 MAC, 9 LGL, 7 HGL)	Guava leaf extract (GLE) (polyphenols: gallic acid, quercetin, etc.)	200 or 500 mg/kg/day, oral, 21 days after DEX (15 mg/kg/day)	28 days	Dexamethason e-induced muscle atrophy	[31]
In vivo animal study	Male C57BL/6 mice (4 wks, HFD-induced obesity)	n=10/group (CON, OB, LSM 200 mg/kg, HSM 500 mg/kg)	Solanum melongena extract (SME) (chlorogenic acid, delphinidin)	200 or 500 mg/kg/day, oral.	12 weeks	High-fat diet–induced obese mice; muscle–brain axis	[32]
In vitro + in vivo	C2C12 myotubes; D-galactose–induced aging mice	40 mice (10/group)	*Polygonatum sibiricum* polysaccharide (PSP)	In vitro: 100–200 μg/mL; In vivo: 100 or 200 mg/kg/day.	2 months	C2C12 mitochondrial assays; D-gal aging mouse model	[33]
In vivo (animal) + exercise	Male C57BL/6J mice	n=8/group; 4 groups (total 32)	*Kaempferia parviflora* extract (polymethoxyfl avones)	Diet with 3% KPE (w/w)	8 weeks	Sedentary vs voluntary wheel running ± KPE (C, K, E, KE)	[34]
Network pharmacol ogy + in vivo validation	Mice (HFD-induced sarcopenic obesity model)	n=8/group; 4 groups (total 32)	Resveratrol (stilbene polyphenol)	N/A	N/A	High-fat diet model; RSV intervention; grip strength, serum lipids, cytokines	[35]

Note: Due to incomplete specifications in some articles about sample size, dosage, and duration, "Not specified" is used where the information is unavailable.

Thirteen studies (Table 2) have demonstrated that diverse phytochemicals, including flavonoids such as apigenin, hesperidin, and quercetin, polyphenols such as resveratrol and guava leaf extract, botanical extracts such as Agastache, nutmeg, and Kaempferia parviflora, as well as other natural products including propolis, shiikuwasha, Solanum melongena, and Polygonatum sibiricum, play important roles in maintaining skeletal muscle health. These compounds act through multiple molecular pathways, including mTOR, PI3K Akt signaling, FoxO3a, AMPK activation, mitochondrial biogenesis, ubiquitin proteasome inhibition, and regulation of myokines, which together contribute to the prevention of atrophy, enhancement of muscle mass and function, improvement of mitochondrial dynamics, and reduction of oxidative stress and inflammation.

Collectively, these findings suggest that phytochemicals hold significant potential as functional foods or nutraceuticals for managing sarcopenia, sarcopenic obesity, glucocorticoid-induced muscle atrophy, and aging-related muscle decline.

Table 2 Studies included in qualitative synthesis

Phytochemical / Extract	Primary Molecular Pathways	Effects on Skeletal Muscle	Potential Applications	Ref.
Apigenin (Flavonoid)	Activates p70S6K via mTOR pathway; no effect on SIRT1, SIRT3, CD38, or adipose browning genes; no effect on cardiac oxidative stress	Prevents muscle atrophy and fibrosis; reduces serum triglycerides; has no effect on obesity, cardiac hypertrophy, or dyslipidemia	Adjunct therapy for sarcopenia associated with obesity and aging; further studies needed on bioavailability and formulation	[23]
Resveratrol + Quercetin (polyphenol)	Inhibits MYOST, ActRIIA, ActRIIB; increases Smad7; enhances Akt phosphorylation (p-Akt Ser473); restores insulin sensitivity	Reduces visceral fat, blood pressure, triglycerides, and HOMA-IR; increases HDL-C and muscle glycogen accumulation	Combined therapy for sarcopenic obesity and metabolic syndrome: potential polyphenol-based supplementation	[24]
Hesperidin	IGF-1/AKT/mTOR, FoxO3a, inflammaging modulation	Enhances muscle mass, strength, and fiber size	Nutritional supplementation for the elderly	[25]
Agastache	Akt/FoxO3a, VEGF, myogenin	Increases cross-sectional area (CSA) and mitigates anabolic resistance	Adjunct to exercise interventions	[26]
Propolis	Nrf2/HO-1, Bax/Bcl2, MAFbx/MuRF1	Attenuates muscle atrophy and improves strength	Anti-aging supplementation	[27]
Shiikuwasha	Inhibition of the ubiquitin–proteasome system (MuRF1/Atrogin-1)	Prevents glucocorticoid-induced muscle atrophy	Therapeutic strategy for catabolic conditions (e.g., sepsis, cachexia)	[28]
Nutmeg	Restores MYH1, MYH4, ACTA1 expression and reduces Hspa1b	Improves soleus muscle mass and exercise performance	Sarcopenia therapy via restoration of contractile proteins	[29]
Standardized *Kaempferia parviflora* Extract (KPE)	PI3K/Akt/mTOR, Mitochondrial Biogenesis (PGC-1α/NRF-1/Tfam), Anti-inflammatory, Antioxidant	Improves grip strength, exercise endurance, muscle mass, fiber size; reduces fat mass and inflammation	Functional ingredient for age-related sarcopenia	[30]
Guava Leaf Extract (GLE)	Ubiquitin-Proteasome System (UPS), mTOR-Autophagy, Apoptosis	Attenuates muscle proteolysis, improves muscle strength, increases CSA, and reduces fat mass	Nutraceutical for glucocorticoid-induced muscle atrophy	[31]
Solanum melongena Extract (SME)	BDNF/PGC-1α/Irisin, Anti-inflammatory, Antioxidant, Myokine Modulation	Improves muscle CSA, reduces oxidative stress and inflammation, enhances myokine secretion	Protection against obesity-induced muscle and brain damage	[32]

Phytochemical / Extract	Primary Molecular Pathways	Effects on Skeletal Muscle	Potential Applications	Ref.
Polygonatum sibiricum polysaccharide	PI3K/Akt/mTOR, mitochondrial function	Ameliorates skeletal muscle aging, restores mitochondrial dynamics	Herbal-based nutraceutical for aging-related sarcopenia	[33]
Kaempferia parviflora extract (additional, animal)	Antioxidant gene expression, plasma antioxidant capacity	Enhances submaximal exercise performance; reduces oxidative stress	Functional food ingredient to improve muscle endurance	[34]
Resveratrol (monotherapy)	AMPK, mitochondrial biogenesis	Improves muscle function, reduces fat infiltration in sarcopenic obesity	Potential therapy for sarcopenic obesity	[35]

mTOR : mechanistic/mammalian target of rapamycin, SIRT1 : sirtuin type 1, SIRT3 : sirtuin type 3, CD38 : cyclic ADP-ribose hydrolase enzyme, MYOST : myostatin (a negative regulator of muscle growth), ActRIIA/ActRIIB : activin type IIA/IIB receptor, Smad7 : SMAD family member 7, an inhibitory modulator in the myostatin signaling cascade, Akt (p-Akt Ser473) : protein kinase B phosphorylated at serine 473, IGF-1 : insulin-like growth factor type 1, FoxO3a : forkhead box O subclass O3a transcription factor, VEGF : vascular endothelial growth factor, Myogenin : myogenic differentiation regulator protein, Nrf2 : nuclear factor erythroid 2–related factor 2, HO-1 : heme oxygenase isoform 1, Bax/Bcl2 : apoptosis-associated Bcl-2 family regulators, MAFbx (Atrogin-1) : muscle atrophy F-box protein, also known as Atrogin-1, MuRF1 : muscle ring finger protein type 1, UPS : ubiquitin–proteasome degradation pathway, MYH1 / MYH4 : isoforms of myosin heavy chain proteins, ACTA1 : skeletal muscle alpha-actin (actin alpha 1), Hspa1b : member 1B of heat shock protein family A (Hsp70 group), PI3K : phosphatidylinositol 3-kinase, NRF-1 : nuclear respiratory factor 1, Tfam : transcription factor A, mitochondrial, BDNF : brain-derived neurotrophic factor, Irisin : exercise-induced myokine, cleaved product of FNDC5, IL-6 : interleukin 6, a multifunctional cytokine, FGF21 : fibroblast growth factor 21, AMPK : AMP-activated protein kinase.

3.1. Molecular Pathways targeted by phytochemicals

The included studies demonstrate that phytochemicals confer protection against sarcopenia by simultaneously targeting multiple, interconnected molecular pathways (Figure 2). Rather than acting on a single mechanism, compounds like flavonoids, polyphenols, and botanical extracts exhibit pleiotropic effects, modulating anabolic signaling, proteolysis, mitochondrial health, oxidative stress, and inflammation. This multi-targeted approach is a significant advantage over single-pathway pharmacological agents.

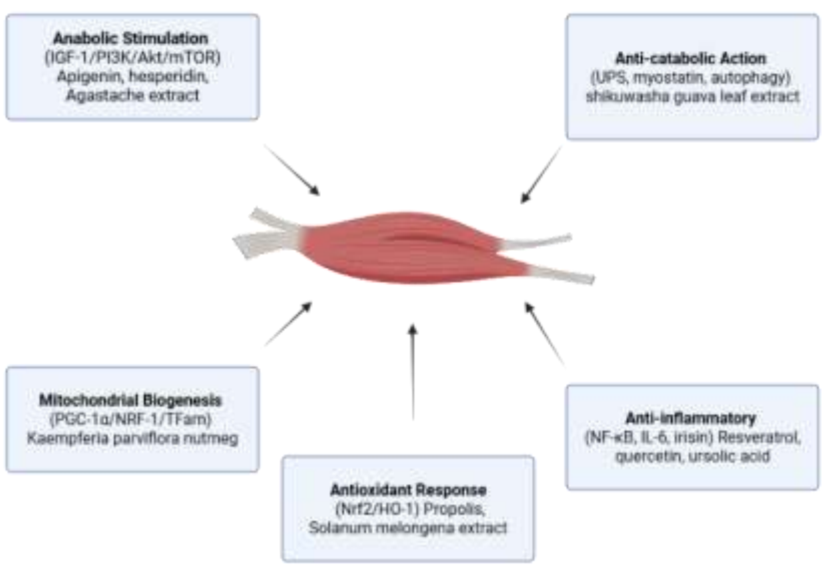

Figure 2. Integrated molecular mechanism of phytochemicals in sarcopenia prevention

Figure 2. Integrated molecular mechanisms of phytochemicals in sarcopenia prevention. Phytochemicals target key pathways in muscle homeostasis: 1) Anabolic Stimulation (IGF-1/PI3K/Akt/mTOR): Enhanced by apigenin, hesperidin, and Agastache extract. 2) Anti-catabolic Action (UPS & Autophagy): Suppressed by shiikuwasha and guava leaf extract. 3) Mitochondrial Biogenesis (PGC-1α/NRF-1/Tfam): Promoted by Kaempferia parviflora and nutmeg. 4) Antioxidant Response (Nrf2/HO-1): Activated by propolis and Solanum melongena extract. 5) Anti-inflammatory & Myokine Modulation: Regulated by resveratrol, quercetin, and ursolic acid, reducing NF-κB activation and modulating IL-6, irisin, and myostatin.

3.2. Regulation of Protein Synthesis and Degradation

The most consistent anabolic effects were observed with hesperidin [25] and the combination of resveratrol and quercetin[24]. Hesperidin robustly activated the IGF-1/AKT/mTOR axis, directly translating to increased muscle mass and fiber size. Notably, the resveratrol-quercetin combination employed a dual strategy: not only did it enhance Akt phosphorylation, but it also potently inhibited the myostatin pathway (via ActRIIA/B downregulation and Smad7 upregulation). This dual action on both anabolic and catabolic regulators makes it a particularly promising intervention for sarcopenic obesity, as it also improves metabolic parameters like insulin sensitivity and dyslipidemia [24].

In contrast, apigenin showed a more limited effectiveness, activating mTOR/p70S6K to prevent atrophy but demonstrating no significant effect on obesity or cardiac parameters in the model studied [23]. This highlights that while effective for muscle-specific atrophy, its benefits may not extend to broader metabolic syndromes without combinatorial approaches.

On the catabolic side, shiikuwasha extract [28] and guava leaf extract (GLE) [31] were highly effective in suppressing the ubiquitin-proteasome system (UPS), specifically targeting MuRF1 and Atrogin-1. GLE exhibited a broader mechanism by also modulating mTOR-autophagy and apoptosis pathways, resulting in comprehensive attenuation of proteolysis and an increase in muscle cross-sectional area. The efficacy of these interventions varied with dosage and duration. For instance, longer intervention periods (12-16 weeks) in aged models [32] showed more profound effects on muscle mass and function compared to shorter studies, underscoring the importance of treatment duration in study design.

3.2. Mitochondrial Biogenesis and Energy Metabolism

Mitochondrial dysfunction is a cornerstone of sarcopenia. Standardized Kaempferia parviflora extract (KPE) activated PI3K/Akt/mTOR signaling and PGC-1α/NRF-1/Tfam-mediated mitochondrial biogenesis, improving grip strength, endurance, fiber hypertrophy, and reducing fat mass [30] . Nutmeg extract restored contractile proteins (MYH1, MYH4, ACTA1) and enhanced exercise performance, although its effect was mainly structural [29]. The resveratrol-quercetin combination integrated mitochondrial benefits with systemic metabolic improvements, enhancing insulin sensitivity and glycogen accumulation [24]. However, intervention duration varied substantially across studies (4–16 weeks), and most experiments used rodent models, limiting translation to humans. Furthermore, differences between crude extracts and purified compounds complicate comparisons, especially in terms of bioavailability and dosing strategies.

3.3. Anti-Inflammatory and Antioxidant Mechanisms

Antioxidant and anti-inflammatory properties provide a foundation for the anabolic and mitochondrial effects of phytochemicals. Propolis activated the Nrf2/HO-1 pathway, downregulated MuRF1 and MAFbx, and suppressed apoptosis, thereby reducing muscle atrophy [27]. Solanum melongena extract acted through the BDNF/PGC-1α/irisin axis, linking muscle protection with neuroprotection[32]. Quercetin, resveratrol, and ursolic acid modulated myokines such as IL-6, irisin, and FGF21, showing potential in regulating organ crosstalk [24]. Yet, methodological differences weaken generalizability: studies applied varied doses of resveratrol (20–100 mg/kg), inconsistent intervention periods, and used diverse animal models. These factors create heterogeneity in outcomes and highlight the need for standardized protocols in future trials.[36]

3.4. Limitations and Future Directions

The primary purpose of this review lies in its integration of fragmented evidence into a unified molecular framework for sarcopenia management, highlighting the superior efficacy of combinatorial approaches (e.g., resveratrol with quercetin) and multi-targeted botanical extracts (e.g., Kaempferia parviflora) that act simultaneously on anabolic, catabolic, mitochondrial, and inflammatory pathways.

However, the current evidence is constrained by significant limitations, most notably the exclusive reliance on preclinical animal models, which limits the direct extrapolation of findings to humans. Further complications arise from pharmacokinetic variability across studies, including differences in bioavailability, the use of crude extracts versus purified compounds, and inconsistent intervention durations, which hinder direct comparisons and consensus on optimal protocols. Crucially, the efficacy, optimal dosing, and long-term safety of these phytochemicals in elderly human populations remain largely unknown.

Therefore, future research must prioritize rigorously designed, standardized clinical trials in target populations, especially those with sarcopenic obesity. Subsequent studies should also explore the synergistic potential of defined phytochemical combinations and their integration with exercise, investigate the role of underutilized local botanicals such as Hibiscus sabdariffa L., and conduct detailed dose-response studies alongside developing advanced delivery systems to enhance bioavailability and therapeutic efficacy.

4. Conclusion

Phytochemicals, including flavonoids, polyphenols, and botanical extracts, demonstrate significant potential in preventing sarcopenia by concurrently targeting key molecular pathways such as enhancing anabolic signaling via IGF-1/PI3K/Akt/mTOR, suppressing proteolysis through ubiquitin-proteasome inhibition, improving mitochondrial biogenesis via PGC-1α/NRF-1/Tfam, and reducing oxidative stress and inflammation through Nrf2/HO-1 and NF-κB modulation, with particularly consistent benefits observed from resveratrol-quercetin combinations and Kaempferia parviflora extracts; however, translation to clinical applications requires rigorously designed human trials to standardize dosing, evaluate safety, and explore the synergistic potential of multi-phytochemical formulations, especially those derived from local botanicals such as Indonesia's Hibiscus sabdariffa L. or rosele.

5. Acknowledgement

This review is supported by the Directorate of Study and Development, Universitas Indonesia, under Hibah PUTI 2024 (No. NKB-650/UN2.RST/HKP.05.00/2024).

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